Kinetics of Iodination of Phenol & Substituted Phenols by N-Iodosuccinimide

P. S. RADHAKRISHNAMURTI* & Ch. JANARDHANA
Department of Chemistry, Berhampur University, Berhampur 760 007

Received 1 November 1978; revised 23 March 1979; re-revised and accepted 6 December 1979

Kinetics of iodination of phenol and substituted phenols by N-iodosuccinimide (NIS) has been studied. The effect of mineral acid like perchloric acid and neutral salts like sodium perchlorate, potassium chloride, potassium bromide and potassium iodide has been investigated. The reaction has been studied in the presence of aqueous acetic acid, aqueous DMSO and in pure water. The reaction shows first order dependence on [NIS] and fractional order dependence on [substrate] in the concentration range 0.0005M to 0.01M and above 0.01M it shows first order dependence on substrate and it is independent of acid (0.01M to 0.2M). Above 0.2 M [H⁺], the reaction exhibits first order dependence with respect to acid and the dependence with respect to substrate is fractional throughout the range studied (0.0005M to 0.02M) and first order with respect to NIS. The concentration dependence of rate with respect to substrate, the iodinating agent and the behaviour with respect to the acid reveal the following rate law:

\[ \frac{d[NIS]}{dt} = k_1 [NIS][S]^x + k_{1'} [NIS][S]^x [H^+] \]

The order of reactivities is m-cresol > p-cresol > phenol > m-chlorophenol > p-chlorophenol > p-bromophenol > p-nitrophenol. The \( \rho/\alpha^x \) plot and reactivity order indicate that it is a C-iodination process. The order of reactivities in different solvents is aq. DMSO > water > aq. acetic acid. The change in rate with temperature in the range of 30°-40°C has been studied and Arrhenius parameters have been calculated in different solvents.

Results and Discussion

The order of reaction with respect to NIS is found to be one as evidenced by the linear plot of log [NIS] versus time. The pseudo-first order rate coefficient is independent of the initial [NIS] in the range 0.0005 to 0.001M.

The order with respect to the different substrates studied is fractional in the concentration range 0.002M to 0.01M; at concentration > 0.01M the reaction exhibits unit dependence with respect to [substrate] (Table 1). This is also confirmed from the linear plots of log \( k_1 \) versus log [S].

A twenty-fold increase in acidity from 0.01M to 0.2M HClO₄ does not affect the rate indicating an apparent independence on acidity. But above 0.2M HClO₄ the reaction exhibits direct unit dependence with respect to HClO₄ (Table 2). The effect of varying ionic strength is negligible.

Effect of varying [substrate] on the reaction rate where there is acid dependence — An increase in [substrate] at higher acidities enhances the reaction rate constant in the concentration range of 0.5 to 20.0 \( \times \) \( 10^{-3} \) M. The plot of log \( k_1 \) versus log [S] is linear with a slope of less than unity indicating fractional dependence with respect to substrate.

In dipolar aprotic solvent like DMSO, the reaction shows first order dependence on NIS, fractional order dependence on phenols in the range 0.002M to 0.01M and is independent of change of acidity in the range 0.5 to 5.0 \( \times \) \( 10^{-4} \) M reaction rate is faster in aq. DMSO than in aq. acetic acid.

In pure water the order with respect to substrate is fractional in the range 0.002M to 0.01M (Table 3),
TABLE 1 — EFFECT OF VARYING [SUBSTRATE] ON REACTION RATE CONSTANT

\[
\begin{array}{ccc}
[NIS] = 0.0005M; [HClO] = 0.01M; [NaClO] = 0.01M; \\
\text{temp.} = 35^\circ\text{C}; \text{solvent} = 10\% \text{HOAc-90}\% \text{H}_2\text{O (v/v)} \\
10^8 [\text{Substrate}] & 10^4 k_1 & 10^4 k_2 \\
M & (\text{sec}^{-1}) & (\text{litre} \text{mol}^{-1} \text{sec}^{-1}) \\
\hline \\
\text{PHENOL} & & \\
2.545 & 3.471 & \\
5.09 & 5.448 & \\
7.635 & 6.555 & \\
10.17 & 8.138 & 8.002 \\
14.29 & 10.39 & 7.256 \\
20.46 & 16.15 & 7.894 \\
\hline \\
p-CRESOL & & \\
1.349 & 3.266 & \\
2.353 & 4.690 & \\
4.930 & 5.995 & \\
10.630 & 8.759 & 8.239 \\
15.21 & 12.14 & 7.982 \\
19.86 & 16.08 & 8.097 \\
\hline \\
p-CHLOROPHENOL & & \\
2.256 & 1.04 & \\
4.005 & 1.688 & \\
8.640 & 2.123 & \\
\hline \\
p-BROMOPHENOL & & \\
2.890 & 1.075 & \\
4.827 & 1.748 & \\
7.28 & 2.04 & \\
10.23 & 2.486 & 2.431 \\
20.00 & 4.47 & 2.236 \\
\hline \\
m-CHLOROPHENOL & & \\
2.517 & 2.456 & \\
5.000 & 0.2870 & \\
7.515 & 0.3771 & \\
10.75 & 0.4827 & 0.448 \\
15.09 & 0.6370 & \\
19.84 & 0.828 & 0.417 \\
\hline
\end{array}
\]

The order of reactivity in different solvents follows the order \( \text{aq. DMSO} > \text{water} > \text{aq. acetic acid} \). The enhancement of rate in the presence of DMSO compared to water presumably is because of the peculiar nature of dimethyl sulphoxide as a dipolar aprotic solvent. It appears that specific solvent effects are operating and the reaction is not linearly influenced by the change in dielectric constant which is also clear from the parabolic plots of \( \log k_1 \) versus 1/D.

Effect of structural variation — It is evident from the data in Table 4 that electron releasing groups enhance the rate constant and electron withdrawing groups decrease it. The \( k_1 \) values refer to the range where there is fractional dependence in substrate. Hence
from the intercept of the double reciprocal plot of $1/k_1$ versus $1/[S]$ the apparent decomposition constants have been obtained for all the substrates and have been used in the plot of log [decomposition rate] versus $\sigma^+$ to explain structure reactivity. Such a plot for different substituted phenols in 10% acetic acid-90% water (v/v) is scattered. It has been established that C-iodination and not O-iodination followed by isomerisation to ortho-para isomers is the preferred reaction. In the present study also it is the C-iodination and not O-iodination which is taking place. This is further confirmed by an additional evidence as follows:

Because the site of attack by the iodinating agent is ortho to the -OH group the $\sigma^+$ value for meta-substituent is used for para-substituted derivatives and the $\sigma^+$ value for para-substituent is used for m-substituted derivatives. Taking this into consideration, the plot of log [decomposition rate] versus $\sigma^+$ is linear with a $p^+$ value of -2.00 for aq. acetic acid system (Fig 1). This $p^+$ value is agreeable with the $p^+$ value obtained using log $k_1$ also instead of log [decomposition rate] in the $p^+$/+$\sigma^+$ plot as the dependence on substrate though fractional is uniformly the same (Fig.1). The order of reactivity of different substituted phenols is m-cresol>p-cresol>phenol > m-chlorophenol > p-chlorophenol ~ p-bromophenol>p-nitrophenol. The applicability of $\sigma^+$ values to prove the point of attack has been earlier invoked by Behrman and Venkataramanan and also successfully utilised by us in the iodination of phenol by molecular iodine as well as aq. acetic acid systems in the temperature range 30° to 40°C, which makes the isokinetic relationship valid for this series. In the case of 10% DMSO-90% H$_2$O (v/v) $\beta$ comes out to be ~27°C. In this connection it might be noted that in the interpretation of enthalpy-entropy relationship great caution is necessary. Such an anomaly in the application of isokinetic relationship has been pointed out by Behrman.

Because the site of attack by the iodinating agent is ortho to the -OH group the $\sigma^+$ value for meta-substituent is used for para-substituted derivatives and the $\sigma^+$ value for para-substituent is used for m-substituted derivatives. Taking this into consideration, the plot of log [decomposition rate] versus $\sigma^+$ is linear with a $p^+$ value of -2.00 for aq. acetic acid system (Fig 1). This $p^+$ value is agreeable with the $p^+$ value obtained using log $k_1$ also instead of log [decomposition rate] in the $p^+$/+$\sigma^+$ plot as the dependence on substrate though fractional is uniformly the same (Fig.1). The order of reactivity of different substituted phenols is m-cresol>p-cresol>phenol > m-chlorophenol > p-chlorophenol ~ p-bromophenol>p-nitrophenol. The applicability of $\sigma^+$ values to prove the point of attack has been earlier invoked by Behrman and Venkataramanan and also successfully utilised by us in the iodination of phenol by molecular iodine as well as aq. acetic acid systems in the temperature range 30° to 40°C, which makes the isokinetic relationship valid for this series. In the case of 10% DMSO-90% H$_2$O (v/v) $\beta$ comes out to be ~27°C. In this connection it might be noted that in the interpretation of enthalpy-entropy relationship great caution is necessary. Such an anomaly in the application of isokinetic relationship has been pointed out by Behrman.

**Table 5 - Activation Parameters**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$E_a$ (kJ mol$^{-1}$)</th>
<th>$\Delta H_f^\circ$ (kJ mol$^{-1}$)</th>
<th>$\Delta S_f^\circ$ (J mol$^{-1}$ K$^{-1}$)</th>
<th>$\Delta G_f^\circ$ (kJ mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td>57.46</td>
<td>54.87</td>
<td>6.47</td>
<td>129.7</td>
</tr>
<tr>
<td>p-Cresol</td>
<td>57.46</td>
<td>54.87</td>
<td>6.51</td>
<td>128.9</td>
</tr>
<tr>
<td>p-Chlorophenol</td>
<td>57.46</td>
<td>54.87</td>
<td>6.47</td>
<td>129.7</td>
</tr>
<tr>
<td>p-Bromophenol</td>
<td>57.46</td>
<td>54.87</td>
<td>6.47</td>
<td>129.7</td>
</tr>
<tr>
<td>p-Nitrophenol</td>
<td>57.46</td>
<td>54.87</td>
<td>6.47</td>
<td>129.7</td>
</tr>
<tr>
<td>m-Chlorophenol</td>
<td>57.46</td>
<td>54.87</td>
<td>6.47</td>
<td>129.7</td>
</tr>
</tbody>
</table>

In pure water at 35°C

| Phenol            | 52.23                | 49.65                             | 5.78                                     | 143.0                            |
| p-Cresol          | 52.23                | 49.65                             | 5.84                                     | 141.8                            |
| p-Chlorophenol    | 52.23                | 49.65                             | 5.84                                     | 141.8                            |
| p-Bromophenol     | 52.23                | 49.65                             | 5.84                                     | 141.8                            |
| p-Nitrophenol     | 52.23                | 49.65                             | 5.84                                     | 141.8                            |
| m-Chlorophenol    | 52.23                | 49.65                             | 5.84                                     | 141.8                            |

In 10% DMSO + 90% H$_2$O (v/v) at 35°C

| Phenol            | 38.31                | 35.75                             | 3.57                                     | 208.7                            |
| p-Cresol          | 38.31                | 35.75                             | 3.64                                     | 207.8                            |
| p-Chlorophenol    | 38.31                | 35.75                             | 3.64                                     | 207.8                            |
| p-Bromophenol     | 38.31                | 35.75                             | 3.64                                     | 207.8                            |
| p-Nitrophenol     | 38.31                | 35.75                             | 3.64                                     | 207.8                            |
| m-Chlorophenol    | 38.31                | 35.75                             | 3.64                                     | 207.8                            |

In 10% DMSO + 90% H$_2$O (v/v) at 35°C

**Fig. 1** — Plot of log (decomposition constant) versus $\sigma^+$ [1, Phenol; 2, p-cresol; 3, m-chlorophenol; 4, p-chlorophenol; 5, p-bromophenol; 6, p-nitrophenol]

**Fig. 2** — Plots of $\Delta H_f^\circ$ versus $-\Delta S_f^\circ$ (a), aq. acetic acid system; (b), aq. DMSO system. [Arabic numerals on the curve refer to phenols listed in Fig. 1]
Mechanism of iodination of phenols — In different solvents like 10% acetic acid-90% water (v/v), pure water and 10% DMSO-90% water (v/v) the general rate law for phenol and different substituted phenols is:

\[ \frac{d[NIS]}{dt} = k_1 [NIS][Phenol]^x + k_2 [NIS][Phenol]^x[H^+] \]

Out of the different species of NIS like protonated NIS, neutral NIS and I+ either free or aquated, the possibility of protonated NIS as the reactive species is accounted for by the fact that the reaction is dependent on [H+] > 0.2M HClO₄. Moreover in the absence of H+ and below 0.2M HClO₄ the reaction shows identical rates indicating the participation of neutral NIS in the present reaction. According to Djerassi and Lenk the possibility of a radical mechanism is ruled out. Hence in the present system either the free NIS or the protonated NIS can complex with neutral phenol in an equilibrium step to give an intermediate transition state complex which decomposes by halogen transfer in a rate-determining step to give finally C-iodinated phenols in subsequent fast steps. The highly negative entropy values also favor the formation of a rigid transition state complex. Addition of succinimide has no retarding effect on the reaction rate. Hence taking all the above factors into consideration the detailed mechanism can be envisaged as shown in Scheme I.

Below 0.2M HClO₄:

\[ \begin{align*}
&\text{NIS + S} \quad \underset{k_1}{\longrightarrow} \quad \text{Complex} \\
&\text{Complex} \quad \underset{k_2}{\longrightarrow} \quad \text{Products}
\end{align*} \]

Above 0.2M HClO₄:

\[ \begin{align*}
&\text{NIS + H+} \quad \underset{k'_1}{\longrightarrow} \quad \text{NISH+} \\
&\text{NISH+ + S} \quad \underset{k_3}{\longrightarrow} \quad \text{Complex} \\
&\text{Complex} \quad \underset{k_3}{\longrightarrow} \quad \text{Products}
\end{align*} \]

Scheme I

Derivation of composite rate law — All the facts such as independence and dependence on acidity, change of order with respect to substrate from fractional to unity in the lower range of acidity and only fractional dependence on substrate at higher concentration of acid are rationalised by a composite rate law. Such a discussion has been earlier done by Swain and Crist.

The experiments conducted at various acidities and at different [substrate] reveal that the total nature of the reaction is as follows:

At each acidity the rate of formation of the product \( k_{ArI} \) is linearly dependent on [ArH]. This result requires the expression for \( k_{ArI} \) to take the form of Eq. (2).

\[ k_{ArI} = i + S (ArH) \quad \ldots \text{(2)} \]

The dependence in acidity is given by Eqs (3) and (4)

\[ S = k'' + k_{iv}[H^+] \quad \ldots \text{(3)} \]
\[ i = k_1 + k'[H^+] \quad \ldots \text{(4)} \]

\[ k_{ArI} = k' + k''[H^+] + k'''[ArH] + k_{iv}[ArH][H^+] \quad \ldots \text{(5)} \]

\[
\frac{d[ArI]}{dt} = k_{ArI}[NIS] \quad \ldots \text{(6)}
\]

\[
\frac{d[ArI]}{dt} = k'[NIS] + k'''[NIS][H^+] + k''[NIS][ArH] + k_{iv}[NIS][ArH][H^+] \quad \ldots \text{(7)}
\]

Equation (7) satisfactorily explains all the facts that has been observed. In the absence of second and last terms of Eq (7) the unit dependence on [NIS], independence on [H+] and fractional and unit dependence on [substrate] are explainable. In the absence of first and third terms unit dependence on acid, [NIS] and fractional dependence on [substrate] are explainable.

An attempt has been made to evaluate the constants \( k', k'', k''' \) and \( k_{iv} \) of Eq. (7). In the plots of \( k_1 \) (observed rate) versus [ArH] the slopes obtained for various acidities are plotted against [H+]. This gives a linear plot having a finite intercept and whose slope corresponds to \( k_{iv} \) and intercept corresponds to \( k'''. \) The various intercepts obtained in the plot of \( k_1 \) versus [ArH] are then plotted against [H+]. The plot of intercept versus [H+] is linear whose intercept corresponds to \( k' \) and slope corresponds to \( k'' \).

Thus the values of \( k', k'', k''' \) and \( k_{iv} \) are 2.0 \( \times 10^{-5} \) sec\(^{-1}\), 8.33 \( \times 10^{-8} \) \( M^{-1} \) sec\(^{-1}\), 4 \( \times 10^{-3} \) \( M^{-1} \) sec\(^{-1}\) and 2.5 \( \times 10^{-2} \) \( M^{-2} \) sec\(^{-1}\). The value of \( k'''' \) obtained graphically almost agrees well with the calculated value 4.17 \( \times 10^{-3} \) \( M^{-1} \) sec\(^{-1}\) showing the validity of the application of graphical analysis. Such fractional dependence on phenols has been observed in the chlorination by CAT in acid medium and in the reaction between anilines and CAT near neutral pH.

Effect of chloride, bromide and iodide on the reaction rate constant — The different halide ions like Cl-, Br- and I- have significant effect on the rate constant. Under identical conditions of 0.01M HClO₄, 0.01M NaClO₄, 0.005M phenol and 0.0005M NIS in 10% acetic acid-90% water (v/v), the reaction is extremely fast in 0.005M KBr (Table-6). In the presence of 0.005M KCl the reaction is moderately fast. In the presence of 0.005M KI the reaction is extremely slow. An independent experiment with 0.005M KI and 0.0005M I₂, 0.005M phenol, 0.01M HClO₄, 0.01M NaClO₄ in 10% acetic acid-90% water (v/v) gives rate constant 2.6 \( \times 10^{-8} \) sec\(^{-1}\) which is almost identical with that obtained by taking NIS instead of I₂. Thus it clearly indicates the formation of I₂ in the reaction medium in the presence of KI (Table 6).

In the presence of Cl- ion and Br- ion the formation of interhalogen compounds like ICl and IBr takes place. These are effective iodinating agents. The formation of ICI is analogous to the formation of ICl from chloramines and iodide ions. The halo-
Table 6 — Effect of Added Halide Ions on Rate Constant

\[
\begin{array}{|c|c|c|}
\hline
\text{Halide ion} & 10^4 [\text{halide ion}] M & 10^4 k_1 \text{ (sec}^{-1}) \\
\hline
\text{KCl} & 5.0 & 5.448 \\
\text{KBr} & 5.0 & 12.25 \\
\text{KI} & 5.0 & \text{Instantaneous} \\
\hline
\end{array}
\]


4. Berliner, E., *J. Am. chem. Soc.*, 72 (1950), (a) 4003, (b) 73 (1951), 4307; (c) 78 (1956), 3632; (d) 80 (1958), 856.


